

## **REMARKS**

Following entry of this Amendment, Claims 1, 2, and 66-73 will be pending in the application. Claims 1, 2, and 66-71 have been amended, and Claims 72 and 73 have been added. Support for the language in the newly-presented claims is found in original Claims 1 and 69 and in the specification at page 123 lines 20-24. No new matter is presented in this Amendment.

### **Claim Objections**

In the Office Action of September 9<sup>th</sup> 2004, claims 66, 70 and 71 are objected to for various informalities. Applicants have amended these claims as suggested by the Examiner, and thus believe that the objections to the claims have been overcome.

### **Claim Rejections Under 35 U.S.C. §112**

#### **New Matter Rejection**

Claims 2, 66, and 71 were rejected in the Office Action under 35 U.S.C. §112, first paragraph, as including 'new matter' with respect to the newly added limitations of "the peptide fragment consisting of residues 249-370" and the addition of a "V5 or His6 tag."

Applicants respectfully disagree with this rejection. However, in order to expedite prosecution of the present claims, Applicants have amended Claims 2, 66, and 71 to delete reference to the 249-370 fragment. Claim 71 has also been amended to recite V5 and His6 tag as the Examiner has recommended.

Accordingly, Applicants believe that the Examiner's rejection of Claims 2, 66, and 71 as allegedly containing 'new matter' should be withdrawn.

#### **Enablement rejection**

Claims 1, 2, 66-69, and 71 were rejected in the Office Action under 35 U.S.C. §112, first paragraph, based upon the specification allegedly not providing an enabling description for dimers other than dimers comprising the two fragments of 247-370 or 249-370. The Examiner's position in making this rejection is that a large quantity of experimentation would be required to determine whether the claimed polypeptide dimers have functional activity.

Applicants respectfully disagree with this rejection. Applicants point out that there are a total of only 6 possible combinations of dimers for these claims, namely: 247-370 with 247-370; 247-338 with 247-338; 339-370 with 339-370; 247-370 with 247-338; 247-370 with 339-370; and 247-338 with 339-370. Applicants submit that an undue amount of experimentation would not be required by a skilled artisan to merely determine whether functional activity is retained for a total of 6 combinations of dimers. In fact, one of ordinary skill in the art would thoroughly understand from the specification that these 6 possible combinations could easily be assayed for activity by, for example, using the methods described in Example 9 of the specification.

Furthermore, Applicants have amended the claims herein to more distinctly point out what Applicants regards as their invention. Applicants submit that these claims are enabled and request that this rejection be withdrawn.

Claims 70 and 71 were specifically rejected in the Office Action under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is alleged that the specification does not provide enablement for dimers comprising, as the first peptide the 16 kDa or 5-6 kDa fragment of SEQ ID NO:2, and as the second peptide the 22-25kDa fragment of SEQ ID NO:2. The position taken in the Office Action is that one skilled in the art would not know how to make a number of species that would be commensurate in scope with the claims. Applicants disagree.

Applicants wish to point out that there are a total of only 2 possible combinations of dimers that can be encompassed by these claims, namely a 16kDa portion with a 22-25kDa portion, and a 5-6kDa portion with a 22-25kDa portion. Applicants submit that it would not take an undue amount of experimentation by a skilled artisan to determine whether each of these 2 possible combinations retain functional activity. As amended, Claims 70 and 71 are believed to be fully compliant with 35 U.S.C §112, first paragraph, and accordingly Applicants request reconsideration by the Examiner and withdrawal of the rejection.

#### Indefiniteness Rejections

Claim 1 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, as being indefinite for the following reasons: (a) there is an insufficient antecedent basis for the claim term "the bonded polypeptide,"; (b) the recitation of "dimer comprising at least two peptides" (because the term dimer means two elements); (c) the recitation of "dimer comprising at least two peptides" and "the bonded polypeptide composed of" (as being unclear with regard to what is intended by peptide); (d) the recitation of "the bonded polypeptide composed of" (as being unclear by the term "composed of"); and (e) the recitation of "said polypeptide has a growth factor activity" (as being unclear as to which polypeptide is being referred to by the phrase). While Applicants do not agree, in order to advance the prosecution of this application they have addressed the Examiner's concerns by amending the claim by deleting "at least two" and "the bonded polypeptide composed of amino acid residues 247-338 and 339-370 of SEQ ID NO: 2" from the claim language and by doing so they believe that the Examiner's concerns have been addressed.

Claim 2 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, for indefiniteness by recitation of "wherein the polypeptide" and for reciting "a composition", which usually has more than one ingredient. Applicants have amended claim 2 by changing "wherein the polypeptide" to "wherein the composition."

Claim 66 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, as being indefinite because it was unclear which fragments were associated with each other to make a protein of 35 kDa. Although Applicants disagree, Claim 66 has been amended by adding "wherein the polypeptide dimers are of about 35kDa", and submit that this language clearly renders Claim 66 'definite' under the cited statute.

Claims 67 and 68 were rejected in the Office Action under 35 U.S.C. §112, second paragraph, as being indefinite because the recitation of "a polypeptide of claim" was unclear. These claims have been amended in the manner suggested by the Examiner, to recite "the polypeptide dimer of claim...", and thus Applicants believe this rejection should be withdrawn.

Claim 69 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, for indefiniteness because of the recitations of "at least two", "composed of", and for lack of clarity with regard to how the peptides are associated to form a polypeptide. Applicants have amended Claim 69 to recite "an isolated polypeptide dimer" and to delete "at least two" and "the bonded polypeptide composed of amino acid residues 247-338 and 339-370 of SEQ ID NO:2", and by doing so believe the claim is now fully compliant with the statute.

Claim 70 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, for indefiniteness due to the recitation of "at least two." Applicants have amended this claim by deleting the recitation of "at least two", and the rejection is believed to be moot.

Claim 71 was rejected in the Office Action under 35 U.S.C. §112, second paragraph, for indefiniteness due to the recitation of "the composition of Claims 1, 2, 66, 69, or 70." Claim 71 has now been amended to read "the composition of Claim 2 or 66 or the polypeptide dimer of Claim 1, 69, or 70." As such Applicants believe that this rejection should be withdrawn.

In view of the amendments to the claims, and the comments contained above, Applicants believe that each ground for rejecting claims 1, 2 and 66-71 under 35 USC §112, second paragraph, have been addressed and overcome. Accordingly, Applicants request reconsideration and the withdrawal of this rejection.

#### **Claim Rejections Under 35 U.S.C. §102(e)**

Claims 1, 2, and 66-71 were rejected in the Office Action of September 9<sup>th</sup> 2004 as anticipated under 35 USC 102 by Gilbert *et al.*, US 6,495,668 B1 ("Gilbert"). Applicants disagree.

The claims before the Examiner recite polypeptide dimers of associated peptide fragments consisting of the C-terminal fragments of SEQ ID NO:2, specifically amino acid residues 247-370, 247-338 and 339-370, where the composition appears under non-reducing conditions as a protein of about 35 kDa; and under reducing conditions as three individual bands, i.e., bands I, II, and III, wherein bands II and III are cleavage fragments of band I; and furthermore where the composition induces proliferation of fibroblasts. The Examiner's attention is directed to Example 12, wherein Applicants show the purification of intact and cleaved products of the 30664188.m99 protein. Under reducing conditions SDS-PAGE clearly indicates three individual bands: band I having a molecular weight of 22-25kDa; band II having a

molecular weight of about 16kDa; and band III having a molecular weight of about 5-6kDa. In addition, as clearly shown in Example 12, N-terminal amino acid analysis of these individual bands clearly indicated that bands I and II begin at residue 247 and band III begins at residue 339. These findings are unique to the present invention.

Nowhere does Gilbert disclose the peptide fragments of amino acid sequence 247-338 and 339-370 of SEQ ID NO:2, each of which Applicants clearly disclose and claim as requirements of their invention. Nowhere does Gilbert disclose a peptide dimer of the associated fragments consisting of amino acids 247-370, 247-338 and 339-370. For these reasons, the claims cannot be anticipated by Gilbert.

As stated to the Examiner in the previous response during the prosecution of this application, Applicants wish to point out that there are multiple factors involved in generating a bioactive PGDF-D peptide dimer composition as encompassed by the present claims. Specifically, peptides have to be expressed, secreted, and assembled to form an active dimer. The ordinarily skilled artisan would have no reasonable expectation of success, and the Examiner has not supported such a position, in predicting whether any particular PGDF-D peptide dimer would have the same or similar bioactivity to those of the present invention based solely on its amino acid sequence. Even minor changes (e.g., addition of one or more amino acids or addition of an affinity tag) at the N-terminus or C-terminus may have very significant effects on dimerization, aggregation and bioactivity. Because of this, it is not scientifically possible to predict from Gilbert which of the many fragments recited in Gilbert are bioactive in the same manner as those of the present invention and which are not. This lack of predictability includes which peptides within Gilbert's '246-370 fragment plus or minus 5 residues' if any, would be bioactive.

As the foregoing makes clear, minor changes in PGDF-D dimers have significant consequences on the operability of PGDF-D peptide dimers. Gilbert provides no basis for selecting between the operable (bioactive) and non-operable embodiments of the many theoretical PGDF-D peptides he lists, and he clearly provides no basis for selecting the particular PGDF-D peptide dimer compositions claimed by Applicants. Once the Examiner appreciates these distinctions, it should become readily apparent that Gilbert clearly cannot anticipate the presently claimed invention.

### **CONCLUSION**

In view of the amendments to the claims and the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Accordingly, they request an early review by the Examiner, a finding of clear patentability, and the passing of this application to issue.

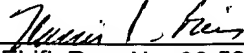
If the Examiner has any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for a three month extension of time and associated fee under 37 C.F.R. §1.17(a)(3) accompanies this response. The Commissioner is authorized to charge any fees that may be due as a

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result of this amendment or the submission of the extension of time, or to credit any overpayment of the same, to Deposit Account No. 50-0311, Reference No. 15966-577 (CURA-77).

Respectfully submitted,



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